Applying New Chemical Assessment Approaches in Human Health Risk Assessment

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ORD, US EPA

SAB/BOSC review
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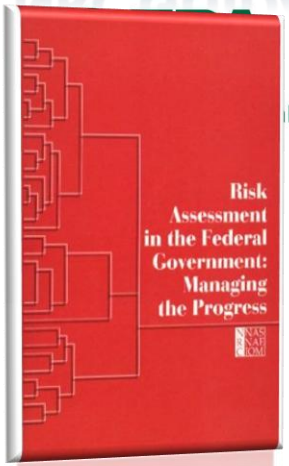
EPA United States Environmental Protection Agency

Outline

- **Human health risk assessment needs and priorities**
- **Synthesis and innovation examples:**
  - Characterizing chemicals lacking toxicity values
  - Priority-setting for evaluation and assessment
  - Applying novel data streams in risk assessments
- **Sustainability assessment tools**
- **Summary**

NRC GUIDANCE:



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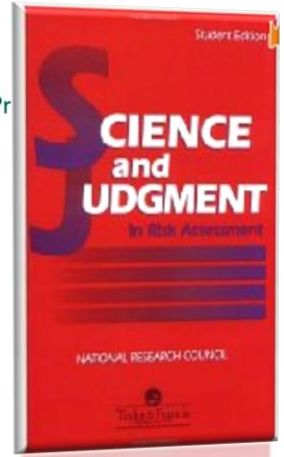

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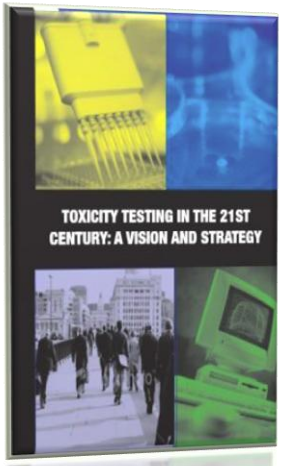

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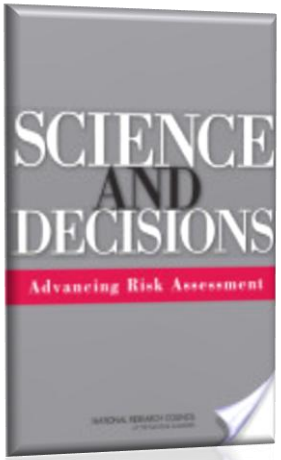
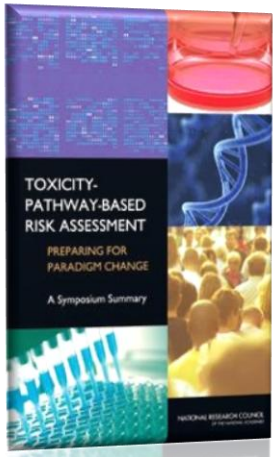
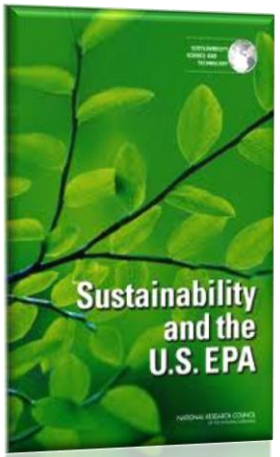


2009



2010



2011

SAB-BOSC GUIDANCE:

- Align with regional and national program office needs, inform decisions
- Bridge gap between ORD's innovative work and the scientific information used for decision-making

EPA STRATEGIC PLAN FOR EVALUATING THE TOXICITY OF CHEMICALS

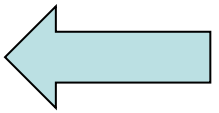
IMPLEMENTATION OF STRATEGIC RESEARCH ACTION PLANS:

Chemical Safety for Sustainability

Human Health Risk Assessment

Human Health Risk Assessment:
Needs and Priorities

- Address risks from chemicals currently lacking toxicity values
- Provide outputs that can be utilized in economic health benefits analyses
- Move beyond single chemical/stressor-based assessments

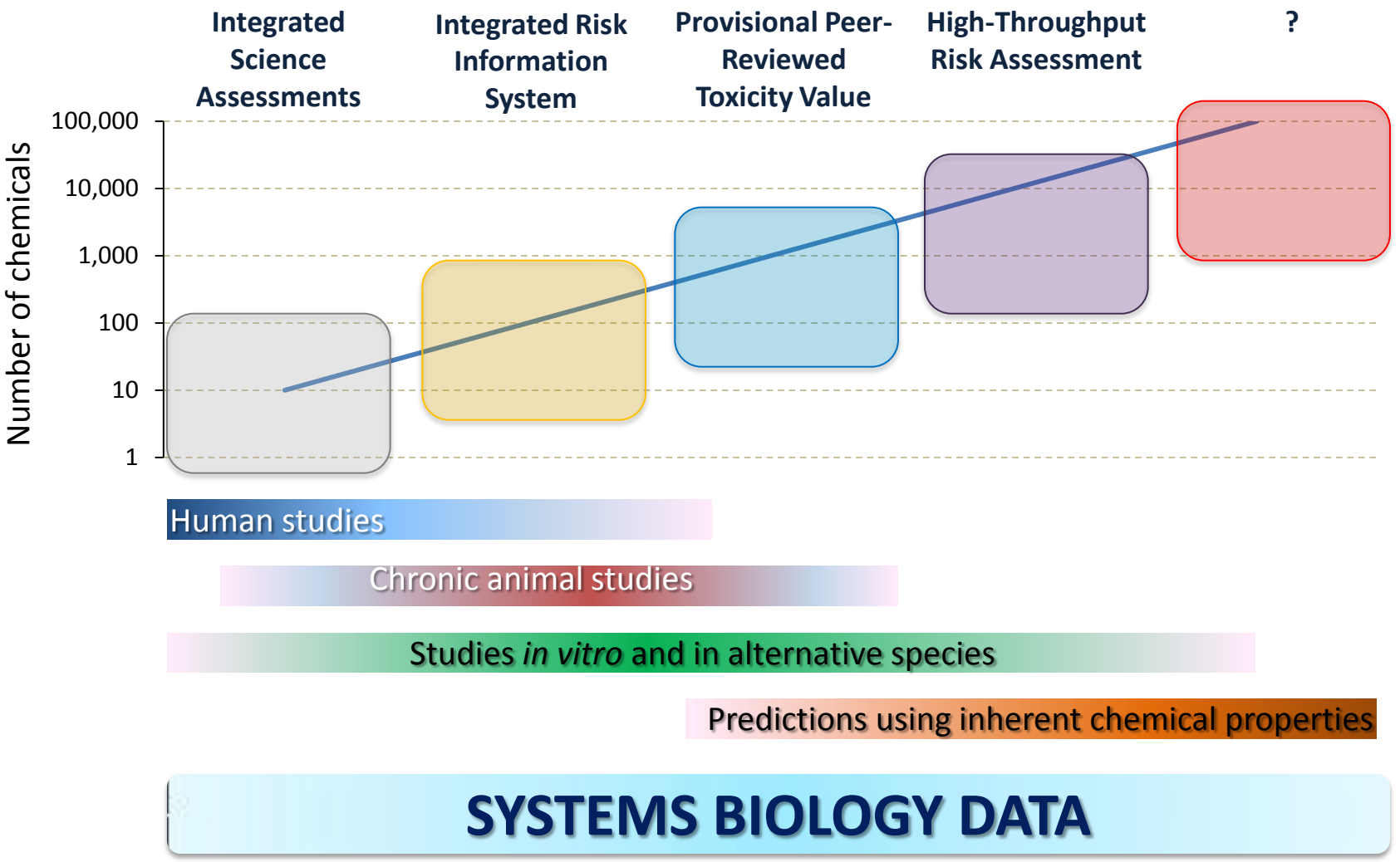


INNOVATION AND INTEGRATION

Human Health Risk Assessment Colloquium Summary Report*:*
http://www.epa.gov/raf/human-health.htm

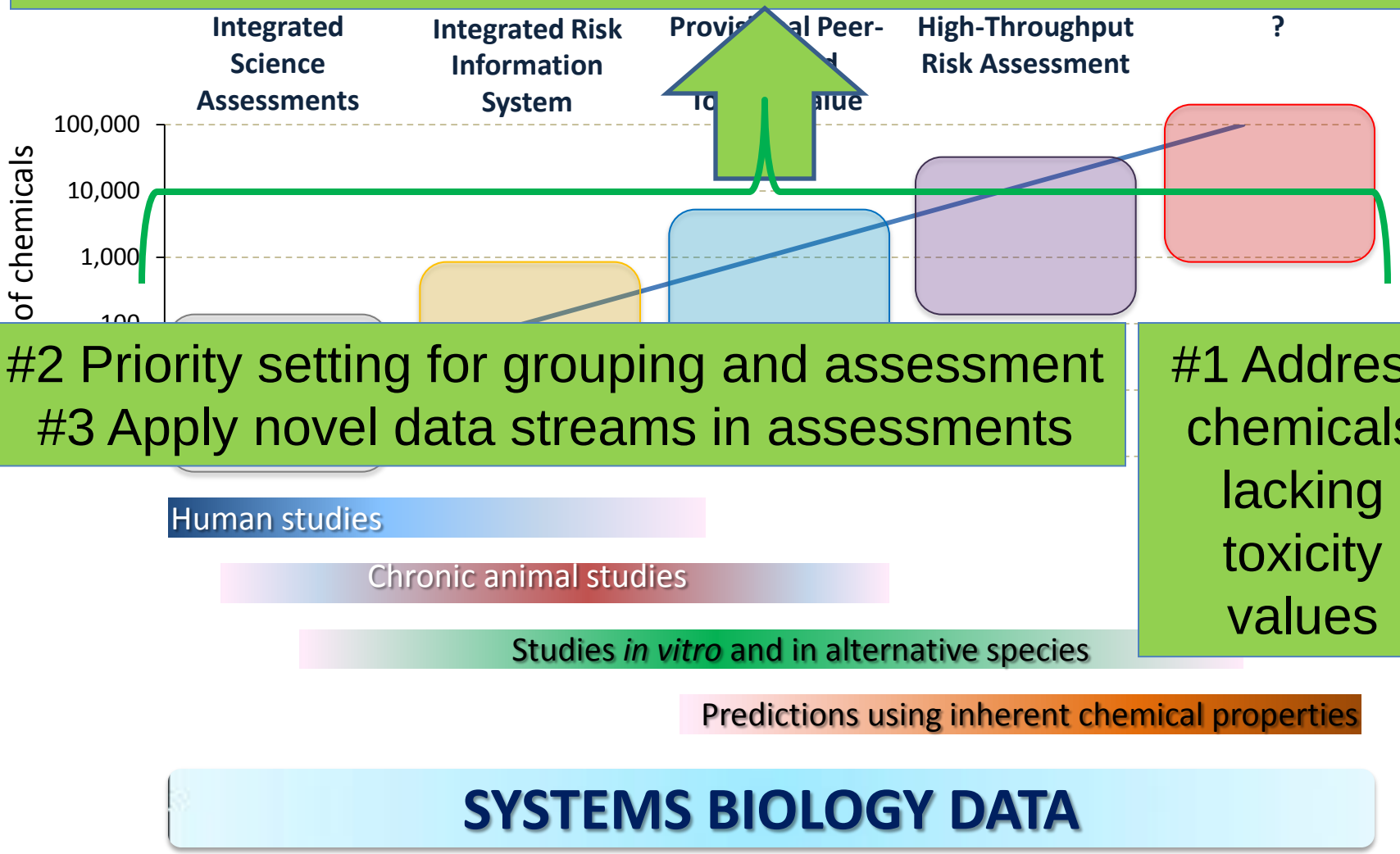
Risk Assessor's "Tool Box":

Decision contexts and data availability drive selection process



Example Integration Products

#4 Using outputs in sustainability analyses



#2 Priority setting for grouping and assessment
#3 Apply novel data streams in assessments

#1 Address chemicals lacking toxicity values

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Example #1: Generating Toxicity Values for Chemicals with Limited Experimental Data:

Conditional Toxicity Value (CTV) Predictor

Conditional Toxicity Value (CTV) Predictor
Rationale and Background

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Chemical of Concern

Are there appropriate *in vivo* experimental animal or epidemiological data?

- No → Is there a known major toxic metabolite responsible for the ultimate toxicity?
  - Yes → Dose-response assessment using either NOAEL/LOAEL or BMDL approach
  - No → **1.** Search for chemicals from 3 surrogate types considering A) Structural, B) Metabolic, and C) Toxicity-like
- Yes → Dose-response assessment using either NOAEL/LOAEL or BMDL approach

Dose-response assessment using either NOAEL/LOAEL or BMDL approach → Yes → **Toxicity Values**

1. Search for chemicals from 3 surrogate types considering A) Structural, B) Metabolic, and C) Toxicity-like

→ **2.** Does the chemical of interest have: A) structurally related chemicals, B) known metabolites or toxicokinetic precursors, C) similar dose-response curves based on TEF* or RPF**, or D) HTS/*in vitro* assays?

- No → STOP
- Yes → **3.** Choose only potential surrogates with repeated dose toxicity values and collect their physicochemical properties.

→ Yes → **4. to 9.** Pool information on surrogates; choose best surrogate based on commonalities, WOE, similarity score and/or most conservative toxicity value; use surrogate toxicity value for chemical of interest

*TEF = Toxicity Equivalent Factor
**RPF = Relative Potency Factor

Adapted from: Wang et al., 2012 *Regul Toxicol Pharmacol*.

Conditional Toxicity Value (CTV) Predictor
Predictive Modeling Approach

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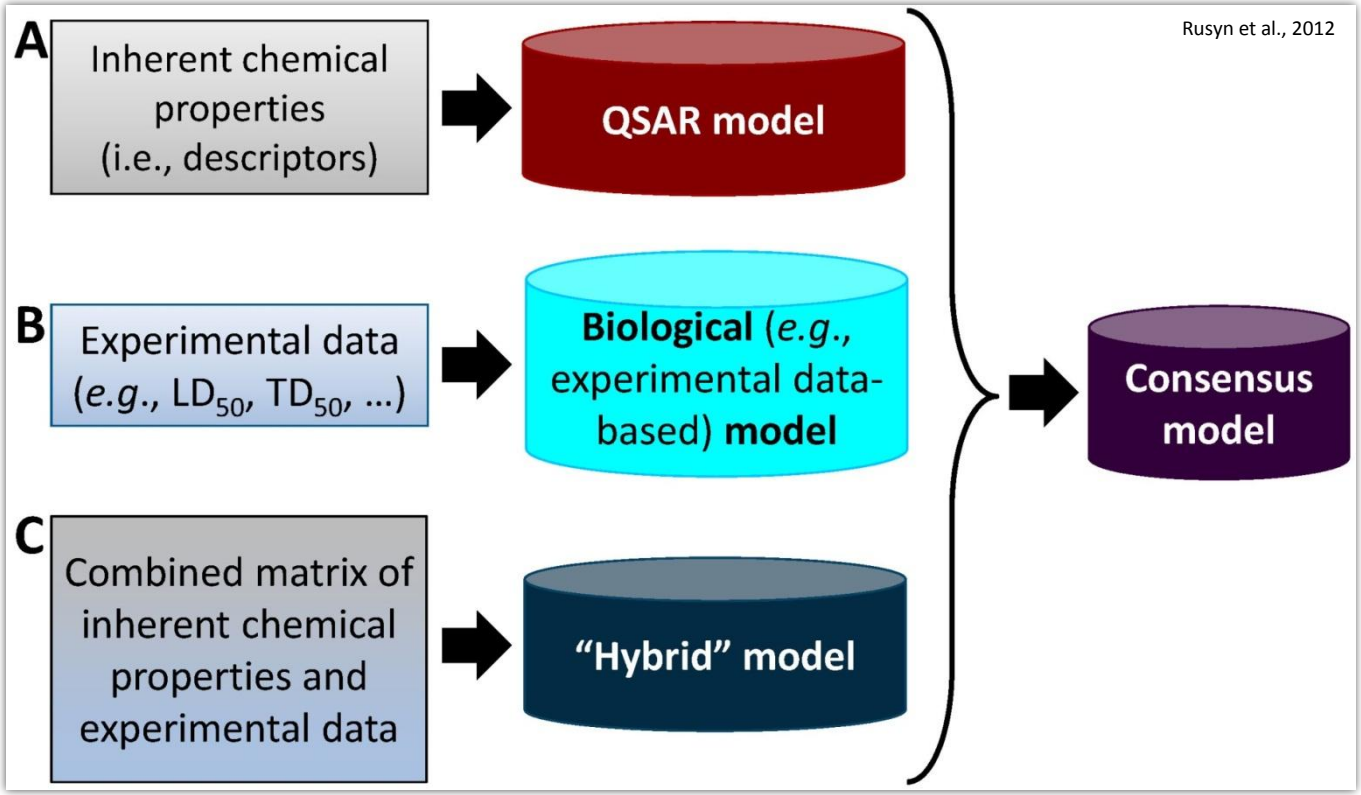
1. Obtain and Curate Data
2. Integrate Data into Matrix
3. Analyze Data and Develop Tools

Data streams for model development



Conditional Toxicity Value (CTV) Predictor

End User Interaction with Dashboard

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End User Input

Step 1: Input compound(s)
- Name, CAS#, SMILES
- Drawing of a structure, etc.

Step 2: Process Input
- Generate ***inherent chemical properties***
- Determine what ***Toxicity Data/Values*** are available

Dashboard

Step 3: Present Options
- Output ***Toxicity Values*** (if available)
- Provide choices to the end user before ***Toxicity Value(s)*** prediction

Step 4: Select Models to Use
- Which CTV? (RfD, CPV, etc)
- What types of models? (QSAR, Biological, Hybrid)

Step 5: Predict Selected Conditional Toxicity Values
- Run selected modeling routines
- Generate (i) numerical outputs, (ii) model performance metrics, (iii) ranked lists, and (iv) graphical representations of the outputs

Outputs

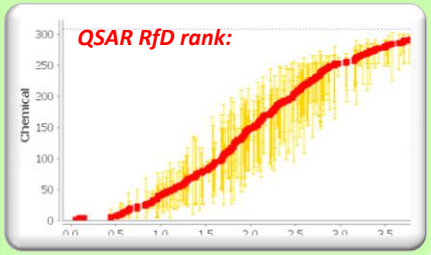
Step 6: CTV Outputs (Toxicity Values and/or PODs for each compound)

QSAR CTV-RfD = 123 mg/kg (within applicability domain)

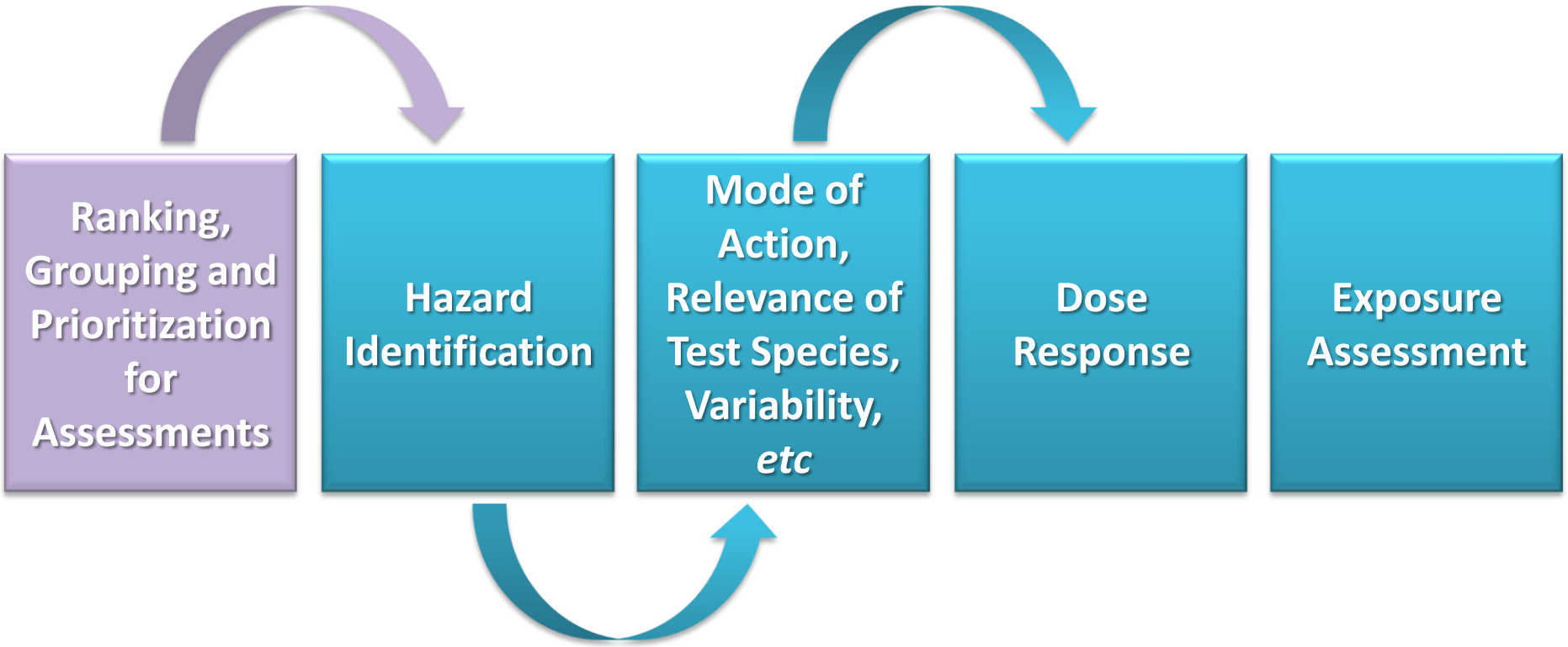
Model performance: *150 chemicals; R^2 = 0.37; MAE = 0.55 log_{10} units dose*

Biological CTV-RfD = 144 mg/kg (within applicability domain)

Model performance: *271 chemicals; R^2 = 0.58; MAE = 0.60 log_{10} units dose*



Basic Components of a Risk Assessment



SYSTEMS BIOLOGY DATA

QSAR qHTS screening	QSAR qHTS screening altern. species	qHTS screening altern. species -omics	*in vitro* data altern. species -omics	Biomonitoring "Exposome"

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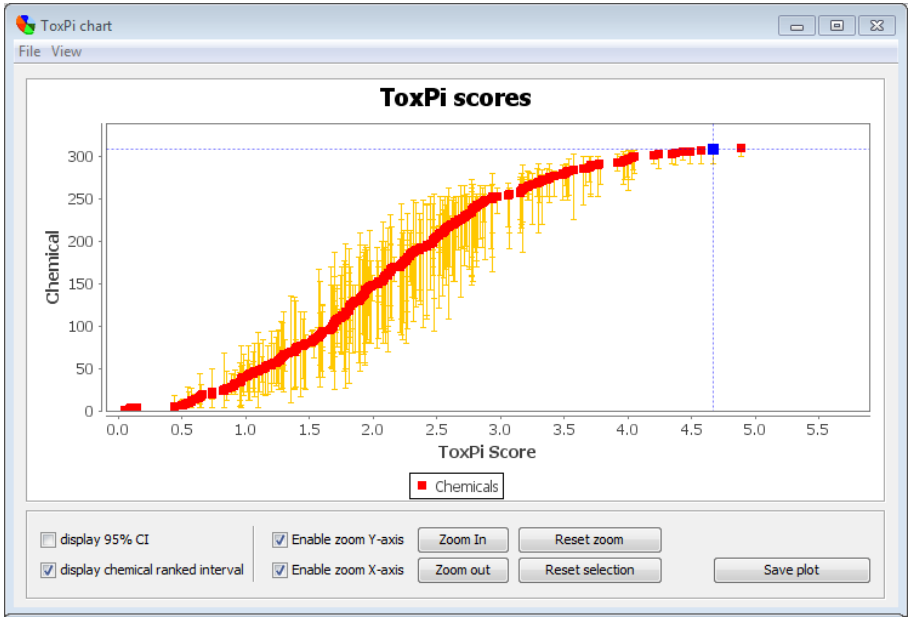
Example #2: Applying Prioritization Tools to Assessment Ranking and Grouping

Chemical Prioritization Tools:

Toxicological Prioritization Index (ToxPi)

- Organizes and integrates information from disparate sources: in vitro, in vivo, pathways and exposure
- ***Potential applications: selecting chemicals for grouping or assessment***



Reif et al. 2010, Env Hlth Persp 118: 1714-1720

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Example #3: Applying Novel Data Streams in Health Risk Assessments

TOX21 *IN VITRO* HUMAN CELL-BASED MODEL:
ADDRESSING CHALLENGES IN HAZARD ID, MODE OF ACTION, DOSE-RESPONSE AND VARIABILITY ANALYSES

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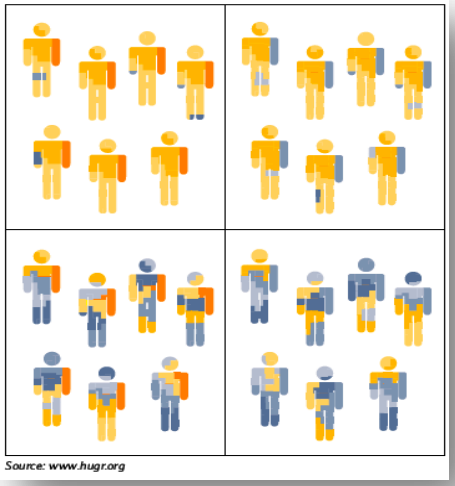
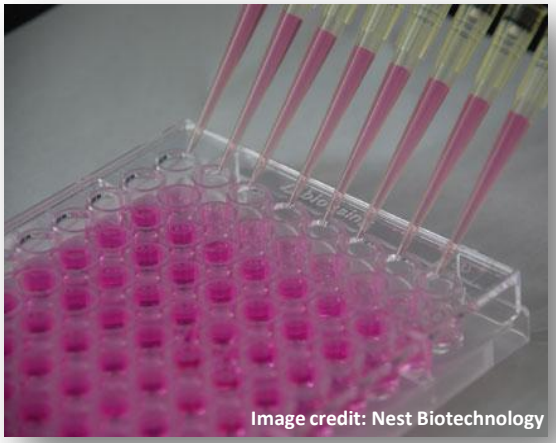
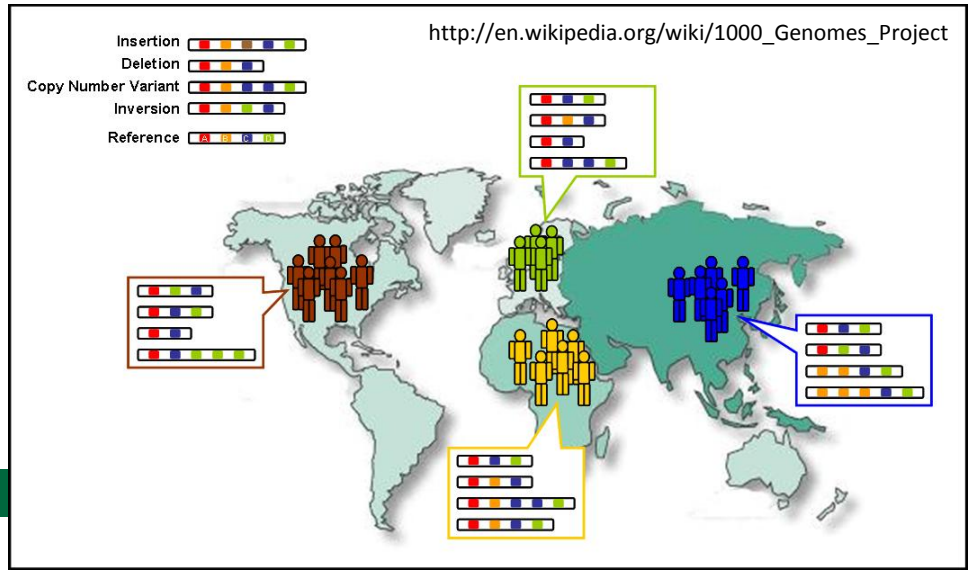


Genetically diverse

Genetically defined



In vitro model system



- The International HapMap Project
- The 1000 Genomes Project

Estimating "Individual" *vs* "population" response

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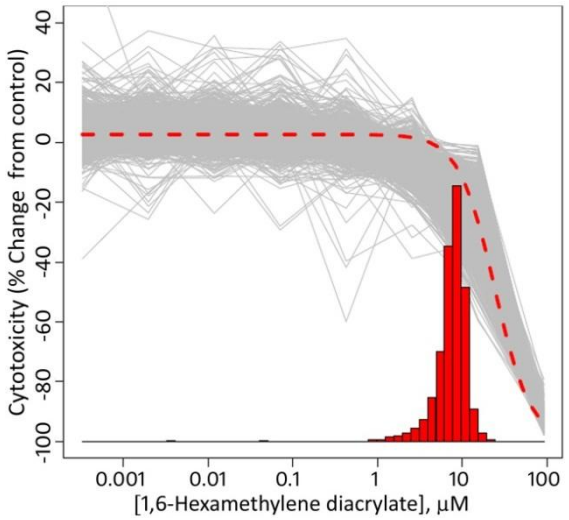
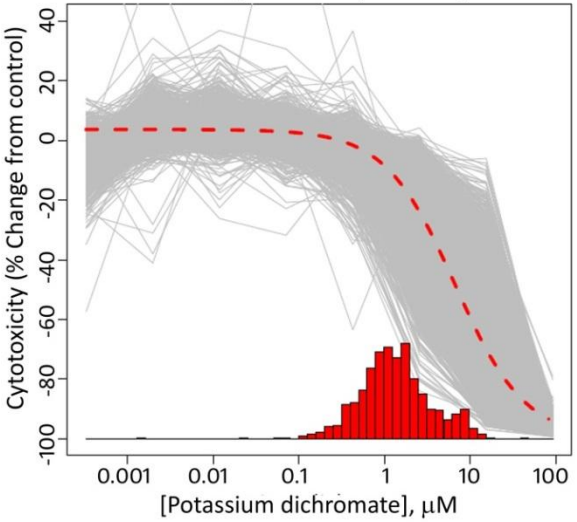
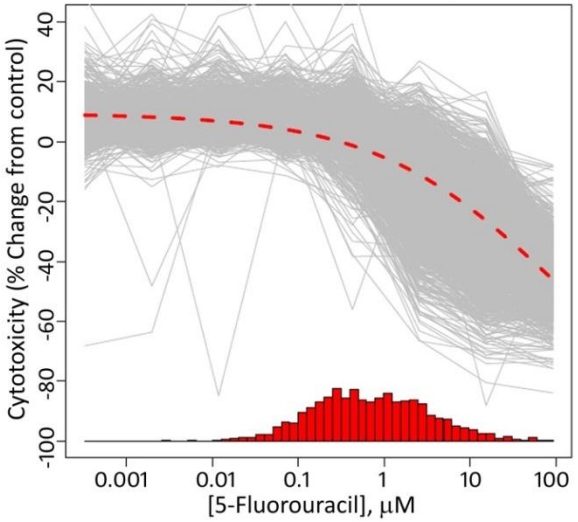
Inter-individual range in EC_{10} (5%-95%): ~3-fold

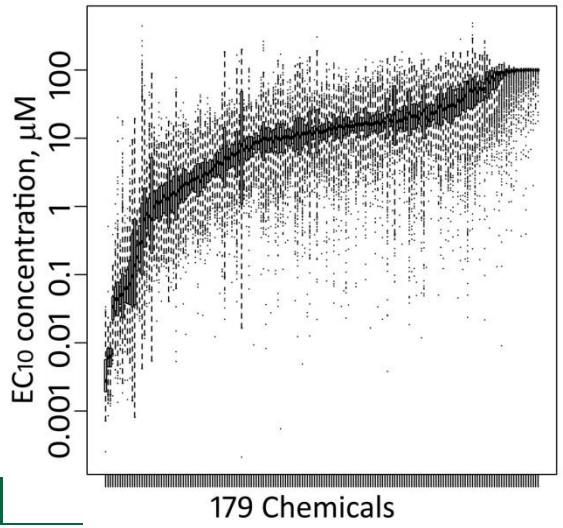


Inter-individual range in EC_{10} (5%-95%):~10-fold

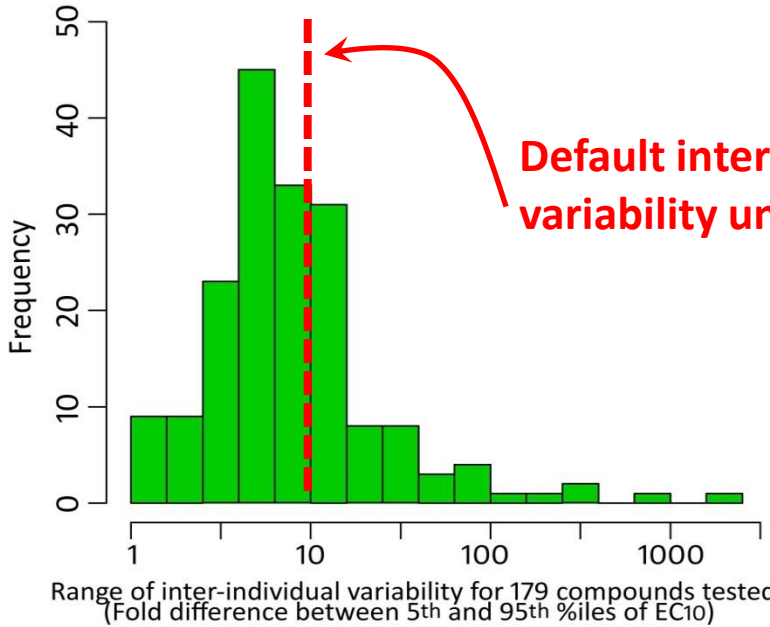


Inter-individual range in EC_{10} (5%-95%):~100-fold



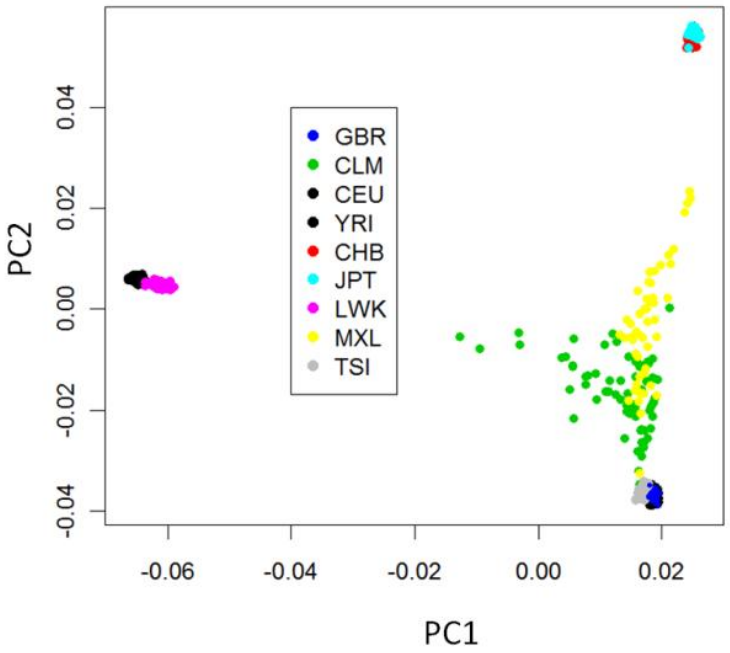


Inter-individual variability in response across cell lines

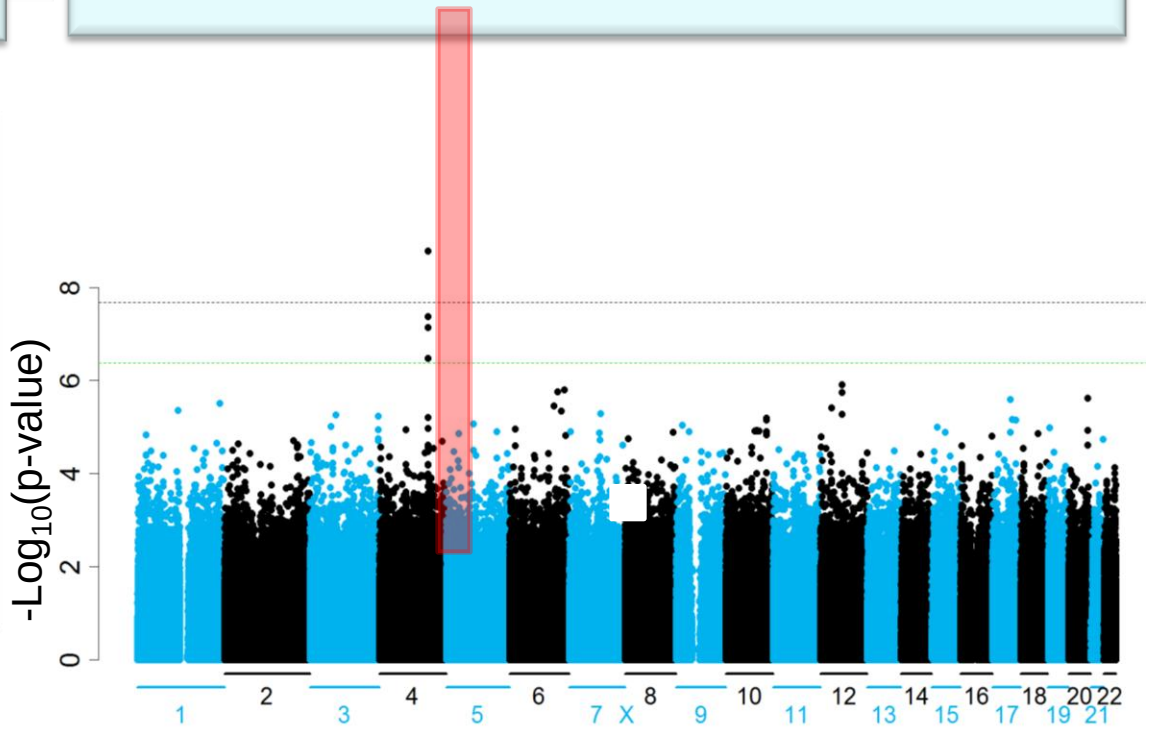


Default inter-individual variability uncertainty factor

Genetic variation across populations



Genome scans aid identification of susceptibility loci



- Additional microarray data for approximately 500 cell lines
- RNA-Seq data being gathered on several hundred lines

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Example #4: Applying Health Hazard Information in Sustainability Tools

Assessing Sustainability:
Comprehensive Environmental Assessment (CEA)

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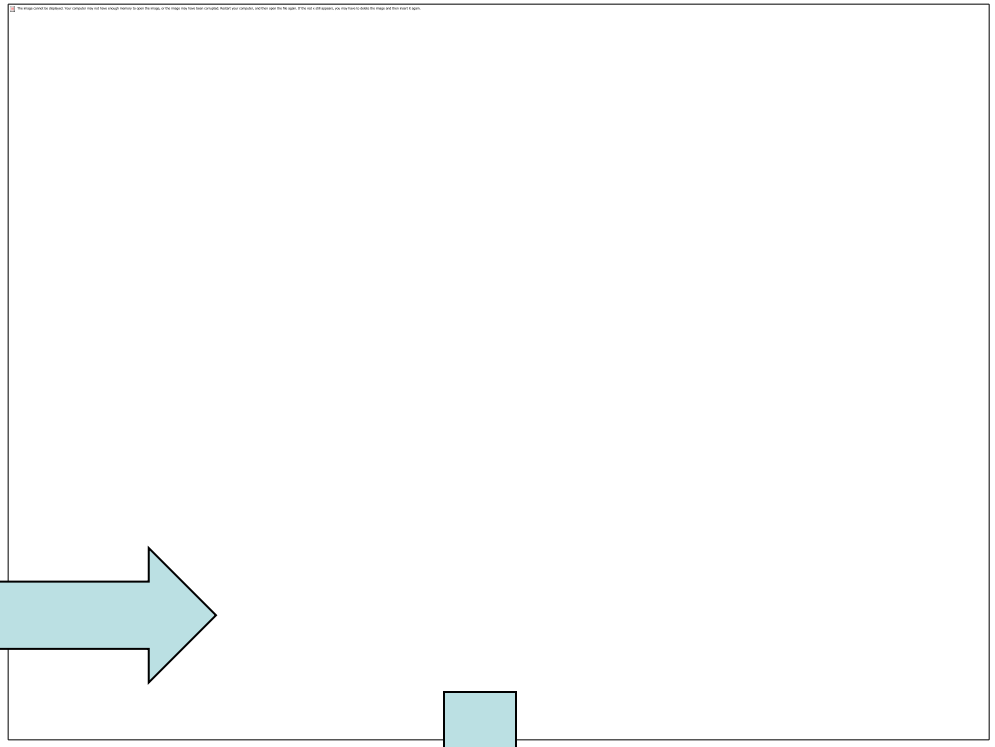

HHRA can provide inputs regarding chemical hazard identification and dose response

CEA outputs:

- Aid evaluation of environmental implications of choices among chemicals, products, and technologies
- Aid identification, prioritization of ORD research
- Enable better targeted decisions

Summary of Integration Goals

Develop innovative approaches to:

- Characterize the toxicity of untested or inadequately tested chemicals
- Set priorities for chemical grouping and assessment
- Apply novel data streams in human health risk assessments
- Inform environmental sustainability and life cycle analyses